CHEMOSENSITIZING WITH LIPOSOMES CONTAINING OLIGONUCLEOTIDES

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Serial No. 09/538,241 filed on March 30, 2000, which is a continuation-in-part of U.S. Serial No.09/354,109, filed July 15, 1999, which is in turn a divisional of U.S. Serial No. 08/957,327, filed October 24, 1997, which claims benefit of priority to Provisional Application Serial No. 60/041,192, filed March 21, 1997. All of these applications are incorporated by reference in their entirety herein.

GOVERNMENTAL RIGHTS

This work was supported by grants from the National Institutes of Health. The United States Government has certain rights in this invention.

FIELD OF THE INVENTION

This invention is related to novel of sensitizing tumor tissue to therapy, preferably chemotherapy or a combination of chemotherapy and radiotherapy using a cationic liposomal composition containing an oligonucleotides or combination of oligonucleotides that specifically binds to a gene expressed by the tumor tissue.

BACKGROUND OF THE INVENTION

The use of chemotherapeutics to treat cancer is well established. Examples of chemotherapeutics finding established application in the treatment of cancers include by way of examples tamoxifen, toremifene, cisplatin, methotrexate, adriamycin, to name but a few. Often such chemotherapeutics are utilized in combination, i.e., as coctails in chemotherapeutic regimens, and often in combination with other types of therapies, e.g., radiation, surgery or antibody-based therapeutics.

While chemotherapeutics have had success in treating a number of different types of cancers, e.g., some leukemia, breast cancer and prostate cancer, chemotherapy is fraught with problems. For example, chemotherapeutics are often only effective against a limited number of cancers. Also, many chemotherapeutics exhibit toxicity to non-targeted tissue, e.g., they may cause nephrotoxicity. Another prevalent problem with chemotherapy is that tumor

Based on these results, it is anticipated that the subject oligo-containing cationic liposomal composition can be used as a means to enhance other chemotherapeutics alone or in combination including by way of example alkylating agents, ~~antimetabolities~~ antimetabolite, apoptosis inducing agents, platinum co-ordination complexes natural products, hormones, hormone antagonists, receptor agonists and receptor antagonists, anthracenedione, substituted area methylhydrazine derivatives, adrenocortcal suppressants, small molecule inhibitors, peptides, antibodies and antibody fragments, enzyme inhibitors and such as tyrosine kinase inhibitors.

Specific examples of such chemotherapeutics include doxorubicin, daunorubicin, methotrexate, adriamycin, tamoxifen, toremifene, cisplatin, epirubicin, docetaxal, paclitatol, Gemzar, gemcitabicine HC1, mixotantrone, and other known chemotherapeutics useful for treatment of cancer.

Examples of cancers wherein the claimed combination therapy is useful include solid and non-solid tumors including those that have metastasized. The therapy can be used for any stage of cancer ranging from pre-cancerous lesions to cancer of advanced stages. Specific examples include prostate cancer, pancreatic cancer, breast cancer, B and T cell leukemias, and lymphomas, bone cancer, head and neck cancer, stomach cancer, bladder cancer, esophageal cancer, lung cancer (e.g. large cell, small cell) ovarian cancer, testicular cancer, myeloma, sarcoma, carcinoma, brain cancer, and others.

In a preferred embodiment the treated cancer will comprise a raf expressing tumor, such as human pancreatic or human prostate cancer and the chemotherapeutic will comprise cisplatin, mixotantrone, epirubicin, gemcitabicine, or Gemzar.

The amount of the chemotherapeutic administrated and the regimen will in general be as is conventional for the particular chemotherapeutic when administered alone or in conjunction with other chemotherapeutics. For example, such dosages may range from about 0.00001 g/kg body weight to about 1-5 g/kg body weight, dependent upon the particular chemotherapeutic and if it is combined with other therapies. The chemotherapeutic agent will be administered prior, concurrent or after administration of the oligo/cationic liposomal composition according to the invention. Preferably, the chemotherapeutic will be administered after the liposomal composition. It is theorized that the subject cationic composition render tumor cells more susceptible to apoptosis. However, the inventors do not want to be bound by their belief.